Thirty-year trends in admission rates for childhood encephalitis in England and impact of improved diagnostics and measles and mumps vaccination– a population based observational study

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Summary

Background: Encephalitis is a serious neurological disorder, yet data on admission rates for all-cause childhood encephalitis in England are lacking. We aimed to estimate admission rates for childhood encephalitis in England over 33 years, to describe trends in admission rates and to observe how these have varied with the introduction of vaccines and improved diagnostics.

Methods: A retrospective analysis of hospital admission statistics for encephalitis for individuals aged 0-19 years was conducted using the English national Hospital Inpatient Enquiry (HIPE, 1979 -1985) and Hospital Episode Statistics (HES, 1990 -2011). Annual age-specific and age standardised admission rates in single calendar years and admission rate trends for specified aetiologies in relation to introduction of polymerase chain reaction (PCR) testing and measles-mumps-rubella (MMR) vaccination.

Results: There were 16571 encephalitis hospital admissions (average hospital admission rate (AR): 5·97/100,000/year (95%CI 5·06-6·82)). Hospital ARs declined from 1979-1994 (annual percentage change, APC, 3·30%; 2·88%-3·66%; p<0·0001) and increased between 1995 and 2011 (APC=3·30%; 2·75%-3·85%; p<0·0001). Admissions for measles and mumps encephalitis decreased by 35- and 60-fold respectively following the introduction of the two-dose MMR vaccine. Hospital ARs for encephalitis of unknown aetiology have increased post-PCR.

Interpretation: Hospital admission rates for all-cause childhood encephalitis in England are increasing. Admissions for measles and mumps encephalitis have decreased substantially. The numbers of encephalitis admissions without a specific diagnosis are increasing despite availability of PCR testing, indicating the need for strategies to improve aetiological diagnosis in children with encephalitis.

Keywords: hospital episode statistics, mumps, measles, MMR, herpes simplex virus

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Introduction

Childhood encephalitis is of significant health importance with long-term morbidity in up to 50% of affected individuals.[1] However, little is known about the epidemiology of all-cause childhood encephalitis in England. This is because previous studies of the epidemiology of encephalitis in England have either involved a specific aetiological group e.g. viral encephalitis,[2] or a predominantly adult population.[3] Understanding the epidemiology in terms of aetiology and time trends is important to aid further understanding of patterns of the disease, gain useful information for future research and aid priority setting in the prevention and treatment of encephalitis.

There have been important innovations that could impact on the diagnosis and prevention of encephalitis. These include introduction of the combined measles, mumps, rubella (MMR) vaccine in the 1980's,[4] use of polymerase chain reaction (PCR) for virus identification, particularly herpes simplex virus (HSV) PCR since the 1990's,[5] and publication of a consensus definition for acute demyelinating encephalomyelitis (ADEM) in 2007. [6] The effect of these innovations on hospital admissions for childhood encephalitis in England is unknown.

We aimed to define hospital admission rates (AR) of childhood encephalitis in England, describe long-term trends in hospital admissions over 30 years and to observe how these have varied with these innovations, using hospital admission statistics data.

Methods

Anonymised data on encephalitis admissions (1979-2011) for individuals <20 years in England were obtained from: (i) Hospital In-Patient Enquiry (HIPE, 1979-1985) and (ii) Hospital Episode Statistics (HES, 1990-2011). Details of these national sources are described elsewhere.[7] Briefly, HIPE contained a random 10% sample of every National Health Service (NHS) hospital admission in England, whereas HES was a complete dataset (100%). For this paper, HIPE numbers are unscaled but the associated rates are scaled to the equivalent of 100%. To provide data on admission trends during 1986-1989, data were also obtained from the Oxford Record Linkage Study (ORLS), a fully linked regional dataset from all NHS hospital admissions in the former Oxford NHS Regional Health Authority area. ORLS data were collected independently of HIPE and HES until 1998, after which the data are a subset of linked HES. All data reported are those for England, unless otherwise stated.

An encephalitis admission was defined by the occurrence of an International Classification of Diseases (ICD) code for encephalitis (Table 1) in any diagnostic position in the hospital record. We analysed the data for 'encephalitis of unknown aetiology' by subtracting ICD codes for encephalitis admissions with a specific diagnosis (including ADEM) from 'all-cause encephalitis'.

Admission records were collected nationally between 1979 and 1998 but were not linked during this period. Admission records only became linkable nationally from 1999 allowing calculation of episode- and person-based rates. For consistent comparisons across the entire study period, episode-based rates are presented throughout. The episode-based AR includes all episodes, regardless of the number of these per person, hereafter termed the "hospital AR". The person-based (first record for each person) rate counts each person once. The latter is the best available proxy for incidence using HES, hereafter termed the "incidence rate" (IR). As a sensitivity analysis, person-based rates were calculated excluding admissions with lengths of stay (LOS) <5 days (excluding deaths), as these might have been individuals with suspected, not confirmed encephalitis. We also sought data on any deaths from encephalitis that occurred without a corresponding HES admission record for encephalitis.

Ethical approval for studying the record linkage datasets was obtained from the Central and South Bristol Multi-Centre Research Ethics Committee (04/Q2006/176). HES data were provided by the NHS Information Centre and its predecessor organisations. In 2013 the NHS Information Centre was reorganised to become the Health and Social Care Information Centre, which then embargoed further provision of datasets to independent researchers.

Analysis

Annual hospital ARs and their 95% confidence intervals (CIs) were calculated using mid-year population estimates from the Office for National Statistics. Summary age standardised admission rates and their 95% CIs were calculated from age-specific rates using the direct method of standardisation and the European standard population.

ARs across five different age groups (<1, 1-4, 5-9, 10-14 and 15-19 years) were compared using the one-way Kruskal-Wallis ANOVA test. The Mann-Whitney *U* test was used to test for differences in ARs between two ICD periods. Annual percentage change (APC) was calculated by Poisson regression, where the APC = (exp (β) - 1)×100 and β represents the model coefficient for year and an additional indicator variable was included to separate the two ICD periods 1979-1994 (ICD-9) and 1995-2011 (ICD-10).

Data were analysed using SAS (V.9.2, SAS Institute Inc, Cary, NC, USA), R (http://www.R-project.com), SPSS (V21) and Graph Pad 6.0, GraphPad Software, La Jolla California USA

Data presentation
Admission rate trends and average hospital AR for all-cause encephalitis and encephalitis of unknown aetiology are reported separately for the two ICD coding periods to account for the transition in codes. Trends for encephalitis diagnoses with sufficiently specific codes in both coding periods and unlikely to have been affected by the transition (ADEM, Herpes, measles, mumps) are reported as continuous data; the average hospital ARs for these were calculated using data from the entire period (1979-2011). Trends for diagnoses with specific encephalitis codes only in the ICD10 (VZV, enterovirus) are presented for only this period.

We compared the hospital ARs for measles and mumps encephalitis before (1979-1985) and after (1990-1995) introduction of the single-dose MMR in 1988 and introduction of a two-dose MMR schedule in 1996 (1997-2011). We compared hospital ARs for herpesviral encephalitis and encephalitis of unknown aetiology pre (1979-1988) and post (1991-2011) introduction of PCR testing.

Role of the funding source

This study had no specific funding. The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. The work undertaken by the Unit of Health-Care Epidemiology in designing and building its multi-purpose, multi-study HIPE and HES datasets was funded by the National Institute for Health Research (grant RNC/035/02). RG's salary is part-funded by Public Health England. MAI's salary is paid through a National Institute for Health Research (EME) grant (HNR00230).

Results

There were 16571 encephalitis hospital episodes (1979-2011). Hospital ARs varied annually (Figure 1) and differed between age groups (p<0·0001), being highest in infants (Appendix, page 1). The average hospital AR (1979-2011) was 5·97/100,000/year (95%CI 5·52-6·41).

Between 1979 and 1994 (ICD9 period), there were 3892 episodes (average hospital AR of 5·65/100,000/year; 4·87-6·42). Hospital ARs declined during 1979-1985 ranging from 5·49-7·63/100,000/year (average: 6·58/100,000/year; 5·92-7·24) and was sustained through the mid-1980s (ORLS data, Figure 1). The decline (1979-1985) occurred in all age groups, although peaks in ARs occurred in 1983 (5-9 years) and 1985 (<1 year and 15-19 years) (Appendix, page 1). Thereafter (1989-1994), hospital ARs were 3·22-8·45/100,000/year (average: 5·78/100,000/year; 5·24-6·32). An overall decline in hospital ARs was observed between 1979 and 1994 (ICD9 period; APC =-3·30%; -2·88% to -3·66%; p<0·0001) (Appendix, page 1).

Between 1995 and 2011 (ICD10 period), 12679 episodes occurred (average hospital AR 6·21/100,000/year; 95%CI 5·65-6·77). Hospital ARs increased (APC=3·30%; 2·75%-3·85%; p<0·0001) (Appendix, page 1) from 4·68/100,000 (4·30-5·07) in 1995 to 8·21/100,000 (7·71-8·71) in 2011, representing a 1·8-fold increase during this period. The increase was wholly in the 0-4 years age group but was most marked in infants (APC=2·79%; 2·05%-3·54%; p <0·01) (Appendix, page 2). The increase in admissions (1995-2011) was mainly in the encephalitis of unknown aetiology group but was also observed for ADEM and 'other' encephalitis (data not shown).

From 1999-2011, there were 10254 encephalitis admissions of 6286 different individuals (0-19 years). In this period, IRs increased (APC=3·41%; 2·81%-4·01%; p<0·0001), ranging between 3·47/100,000/year (95%CI 3·13-3·81) and 4·69/100,000/year (4·31-5·08) (Appendix, page 2), giving an average IR (1999-2011) of 4·02/100,000/year (3·80-4·28). Excluding person-based admissions with LOS <5 days (n=2025), the upward trend persisted (Appendix, page

2) with IRs between 2·54/100,000/year (2·25-2·83) and 3·45/100,000/year (3·12-3·78), giving a recalculated average IR of 2·91/100,000/year (2·80-3·14). There were 122 death certificates mentioning encephalitis, without a corresponding HES record for encephalitis, identified between 1999 and 2011. These 122 deaths add 1.9% to the 6286 people admitted with encephalitis between 1999 and 2011, with no up or downward trend over time,

Before the single-dose MMR (1979-1985), measles encephalitis admissions peaked every 3 years (Figure 2a), average hospital AR: 0·32/100,000/year (95%CI 0·10-0·52). Thereafter (1989-1996), the average hospital AR fell 8-fold (0·04/100,000/year; 0·02-0·06). Following introduction of the 2-dose MMR schedule, the average hospital AR (1997-2011) was 0·009/100,000/year (95%CI 0·003-0·01), corresponding to a 35-fold and 4-fold decrease when compared with before and after the introduction of a single-dose MMR schedule. The post-MMR decrease in hospital ARs was observed across all age groups (Appendix, page 3).

Hospital ARs for mumps encephalitis fell from a pre-single-dose MMR high of 0·91/100,000/year (1983) to a post-single-dose MMR low of almost zero (1991) (Figure 2b). The average hospital ARs for mumps encephalitis differed between the vaccination periods: 0·60/100,000/year (95%CI 0·45-0·90) [1979-1985]; 0·02/100,000/year (0·01-0·03) [1990-1995] and 0·01/100,000/year (0·00-0·01) [1997-2011]; p<0·0001. Compared with the pre-single-dose MMR period, this corresponds to 30- and 60-fold declines in average hospital ARs following the introduction of a single-dose and two-dose MMR vaccine respectively. The post MMR decline was observed across all age groups (Appendix, page 3). A 12-fold rise in mumps admissions occurred between 2004 and 2005, attributable to an increase in the 15-19 years age group.

The average hospital AR for encephalitis of unknown aetiology was 1·93/100,000/year (1·65-2·22) [1979-1994] and 2·91/100,000/year (2·75-3·08) [1995-2011] (Figure 3a). The average hospital AR was 1·99/100,000/year (1·51-2·46) pre-PCR (1979-1989) and 2·73/100,000/year (2·50-2·95) thereafter (1991-2011); p<0·0001.

Pre-PCR, hospital ARs for herpesviral encephalitis (1979-1985), ranged from 0·15-0·41/100,000/year (average:0·23/100,000/year (95%CI 0·10-0·36). Post-PCR (1991-2011), they ranged from 0·33 to 0·68/100,000/year (average: 0·47/100,000/year; 0·43-0·52) (Figure 3b), corresponding to a 2-fold increase (p<0·0001). Hospital ARs for VZV encephalitis (1995-2011) ranged from 0·25/100,000/year (95%CI 0·16-0·34) to 0·61/100,000/year (0·47-0·75) with approximately 3-yearly peaks (Figure 4). Admissions were highest in the 1-4 age group.

Hospital ARs for EV encephalitis (1995-2011) ranged from 0·01 to 0·06/100,000/year (average: 0·09/100,000/year; 95%CI 0·04-0·14) peaking at 0·40/100,000/year in 2002, representing a 20-fold increase from 2001. This peak corresponded to an increase in admissions in the <1year age group and was mostly in females (female vs. male: 0·76/100,000/year vs. 0.06/100,000/year. ARs (2003-2011) decreased but were higher in this period than between 1995 and 2001 (average hospital AR: 0·10/100,000/year (0·06-0·14) vs. 0·03/100,000/year (0·01-0·04) respectively; p<0·0001.

Hospital ARs for ADEM (1979-2011) ranged between 0·18/100,000/year (95%CI 0·11-0·26) and 1·41/100,000/year (0·73-2·09), peaking in 1980, 1983 and 1984 (Figure 5a). ARs (1979-1994) decreased (APC= -3·78%; -2·69 to -4·86; p<0·0001) and thereafter rose steadily (APC=10·55%; 8·76-12·37; p <0·0001) (Figure 5b) from 0·24/100,000/year (0·15-0·32) in 1995 to 1·12 /100,000/year (0·93-1·30) in 2011. ADEM admissions (1979-1985) were mostly in the 1-9 year age group with minimal contribution from the other age groups (Figure 5c-d). Admissions in the 1-9 year age group fell in the early 1990's and were lower than they were in the 1980's. Hospital ARs for ADEM (1995-2011) varied annually, showing an increasing trend in the 1-19 year age group. Admissions in infants were virtually non-existent prior to the 1990's, rising thereafter, with 3-yearly peaks (Figure 4b-4d).

Discussion

This unique 33-year study is the first to report on long-term hospital admission trends for all-cause encephalitis in an exclusively paediatric population in England. It is also the first to quantify impact of the MMR vaccine on measles and mumps encephalitis admissions in England. The data show that, after a decline (1979-1994), admissions for all-cause encephalitis have increased since (1995-2011). The age-related epidemiological profile of ADEM has changed with more infants being admitted with the diagnosis in recent years. Measles and mumps encephalitis admissions have reduced post MMR. Admission rates for herpesviral encephalitis and encephalitis without a specific diagnosis

have increased post-PCR.

While the exact reason for the initial decline (1979-1994) is unclear, it is likely that a major component is the reduction in measles and mumps encephalitis admissions with MMR vaccination (including a reduction in cases of unspecified aetiology that were in fact caused by mumps and measles). The reasons for the increase in all-cause encephalitis in the later years need consideration.. Restriction of this finding to the ICD10 period makes it unlikely to be due to the transition in ICD codes and change in hospital coding practices. Another consideration is whether the increase could be explained by diagnostic displacement with reclassification of cases of 'viral meningitis' as 'viral encephalitis'. This is unlikely since the increase in encephalitis admissions from 1995 is not mirrored by a decrease in viral meningitis cases[7] in the same time period. It is also unlikely that the observed increase in the later years simply represents an increase in multiple admissions per person with encephalitis. The increasing trend was similar using the person-based rates, i.e. only counting each person once, and after adjusting for short hospital stays (which might not have been confirmed encephalitis), indicating a genuine increase in encephalitis incidence. Plausible reasons for this observation include increasing case ascertainment with the discovery of biomarkers such as anti-NMDAR antibodies and other biomarkers implicated in encephalitis,[8] recognition of clinico-radiological syndromes such as limbic encephalitis which would have historically been undiagnosed in some instances[9] and increased awareness and use of diagnostic tools such as EEG in children with unclear infections. There is also the possibility of emergence of new viruses implicated in encephalitis and changing neurovirulence such that pathogens that previously caused meningitis are now causing encephalitis.

Routine use of the MMR vaccine has resulted in reduction in disease burden from measles, mumps and rubella.[7,10] While its specific effect on the incidence of measles and mumps encephalitis has been demonstrated in some countries, [11,12] data for England are lacking. In this study, admissions for measles encephalitis were high prior to the mid 1980's, when the single measles vaccine was being used and when coverage was low (<60%) and insufficient to fully interrupt transmission.[4] Following introduction of the single-dose MMR vaccine in 1988 and an increase in vaccine coverage to > 90%,[4] possibly due to an increase in public awareness, a sustained decline was observed. The increase in measles encephalitis admissions observed in 1994 matches the increase in overall measles case notifications in England in the same year.[13,14] However, contrary to the notification data in which children over 10 years were most affected, admissions for encephalitis in this study were highest in the 1-4 year age group, possibly reflecting greater susceptibility of younger children to complications such as CNS manifestations.[15] Following the introduction of the two-dose MMR schedule in 1996 with vaccine coverage sustained in excess of 80%,[4] admissions for measles encephalitis declined further and have remained very low; this was similar for mumps encephalitis admissions.

Contrary to the measles data, the increase in mumps encephalitis admissions in 2005 mostly affected the 15-19 years age group, which was the predominantly affected age group in the 2005 outbreak in England and Wales.[10,16] Various reasons for the increased infection rate in the 15-19 years age group during the outbreak have been suggested. Most of the infection occurred in children who were not eligible for routine MMR vaccination post introduction in 1988. [16,17] In addition, herd immunity was possibly not sufficient to prevent transmission in this susceptible group.

The changing age-related epidemiological profile of ADEM is notable. ADEM admissions were high in the early 1980's, mostly affecting the 1-9 years age group and were lower in the early 1990's, corresponding to a reduction in admission rates in the same age group. This finding mirrors the data for measles and mumps encephalitis admissions in the 1-9 year age group suggesting that the ADEM rates in the 1980's might have been caused by measles and mumps and the lower rates in the early 1990s possibly reflect the impact of MMR vaccination in reducing measles and mumps infections especially in the 1-9 year age group. The rising trend in ADEM admissions from the mid 1990's most probably indicates enhanced disease recognition with the widespread routine use of MRI scans[18] and increased case ascertainment following publication of a consensus definition guideline in 2007.[6] It may also be a true rise in ADEM cases due to the emergence of pathogens or environmental triggers that are yet to be identified. Interestingly, ADEM admissions are coded in infants from 1990 onwards having been virtually non-existent prior to this time, with admissions occurring in three yearly peaks suggesting an unknown, possibly viral aetiological agent. There is a growing body of evidence showing an association between certain neuronal autoantibodies and acute demyelinating disease in children.[19] Thus the increasing ADEM trend may also reflect improved disease identification through awareness of this association with increasing testing for neuronal antibodies in children

presenting with encephalopathy, where the cause is uncertain. Given the beneficial role of immunotherapy in the management of ADEM,[20] these findings are important since early consideration of this diagnosis, testing for neuronal antibodies and timely institution of immunotherapy could be worthwhile.

Post-PCR, herpesviral encephalitis admissions increased possibly reflecting enhanced aetiological diagnosis. Admissions for encephalitis without a specific diagnosis also increased. Uncertainty about aetiological diagnosis could lead to unnecessary delays in the institution of appropriate treatment, and result in poor outcomes.[21-23]Also, non-identification of a viral cause could lead to the institution of unnecessary treatment and limit appropriate public health prevention and control strategies. The high proportion of cases in this category could reflect the delays in obtaining laboratory results, affecting timely documentation in HES of an aetiological diagnosis. Additionally, variations in the breadth of PCR testing in different hospitals due to lack of a standard diagnostic algorithm for viral encephalitis in England may lead to some aetiologies being missed. There may also be newer pathogens implicated in encephalitis[24] that are either not identified by currently available testing or do not have a specific ICD code. Parechoviruses were only identified as a distinct genus from enteroviruses in 1999 and publication of the most recent ICD version in 1994 predates this. Therefore no specific ICD code exists for this aetiology. In addition specific testing for parechovirus only became available in 2006. It is therefore likely that encephalitis caused by parechovirus would have been coded as unknown aetiology. Similarly there is increasing recognition of autoimmune encephalitis syndromes due to a range of antibodies to neuronal surface antigens.[25-27] These syndromes currently do not have a specific ICD code and may explain the high and increasing proportion of encephalitis admissions assigned to the unknown aetiology group, despite PCR testing. While available guidelines for the management of suspected viral encephalitis[28,29] may help standardise the laboratory diagnostic pathway, there remains an urgent need for research into improving aetiological diagnosis in encephalitis cases.

There are a few comparable paediatric studies. An Australian study in children ≤ 14 years (2000-2012)[30]reports an incidence estimate of 3.8-5.0/100,000 population. A 2-year surveillance conducted in Finland which included children aged 1 month to 15 years reported an incidence of 10.5/100,000 children.[31] A Japanese questionnaire based study (1984-1990) of encephalitis admissions for children ≤ 15 years reported an incidence rate of 3.3/100,000[32] while an earlier study of viral encephalitis in England reported an admission rate of 2.8/100,000 children.[2] Although the incidence rate for all encephalitis cases in this study, irrespective of LOS (i.e. 4.02/100,000 population) is comparable to these studies, it is 2.6 fold lower than that reported in the Finnish study and 1.4 fold higher than was reported in the earlier study in England. The higher admission rates in the Finnish study may be due to the very short study period, which doesn't take into account year-on-year variation seen with encephalitis admissions. The earlier study in England[2] observed admission rates for viral encephalitis alone, which would explain the lower rate reported. A further study in England (2005-2009) of encephalitis admissions in children and adults[3] reported a best incidence estimate of 5.23/100,000 population after accounting for potential over diagnosis of HES only encephalitis cases. This is higher than the recalculated incidence rate in this study of 2.91/100,000 population and possibly reflects differences in the study populations and the methodology used in ascertaining incidence rates from 'true' encephalitis admissions. Of note, deaths from encephalitis without a corresponding HES record for it added only a small fraction to the total number of cases admitted between 1999 and 2011 providing some confidence in our estimation of disease incidence using HES data.

The main strength of this study is the longevity of the datasets, which are excellent resources for observing the impact of developments in the field of encephalitis on long-term admission trends. The use of episode-based data reflects the impact of disease on the NHS, while the use of the linked data helps to reach a truer approximation of disease incidence. However, while the quality and consistency of HES data are generally well established, they are less so for encephalitis, possibly because precise laboratory diagnoses are sometimes not available at the time of discharge.

HES data rely on accurate recording of clinical information in case records and correct coding which can be inconsistent although there is some evidence that this is improving.[33]The difficulty with making a clinical diagnosis of encephalitis, and therefore subjectivity among clinicians, may have an impact on the validity of cases coded in HES. National data for England are lacking between 1986 and 1989; however availability of ORLS data provides some insight to admission trends during this period. The use of different revisions of the ICD codes could impact on estimation of admissions and disease incidence for certain aetiologies. We attempted to avoid this by calculating hospital ARs separately for the two ICD coding periods for aetiologies more likely to have been affected by this

transition. Furthermore, the calculated IR is based on person-based data, which are only available in the ICD10 period. Ultimately, this study is the first of its kind and provides useful data on long-term trends on encephalitis hospitalisations for paediatric population in England and gives some insight to the disease burden on the healthcare system.

Conclusions

Childhood encephalitis admission rates in England declined between 1979 and 1994 but increased between 1995 and 2011. The impact of MMR vaccination may have contributed to the initial decrease, but the exact reason for the later increase is unclear and warrants further investigation. The increasing availability and widespread use of MRI scans, increasing awareness and testing for neuronal autoantibodies and increased diagnostic certainty have probably contributed to the rising trend in ADEM admissions. Strategies to enhance aetiological diagnosis in children with encephalitis are needed.

Research in Context

Evidence before this study

We searched PubMed up to 6th December 2016 for papers reporting on encephalitis disease trends. We used the search terms "encephalitis" AND ("incidence rate" OR "incidence estimates" OR "hospital admissions" OR "hospital admission rates" OR "admission rates" OR "hospitalisations" OR "hospitalizations" OR "hospital episode statistics")

We reviewed studies reporting incidence of encephalitis either from microbiological surveillance data or hospital admission statistics. We also reviewed references of such articles to identify those not picked up by the original search. Several studies were identified in Australia, East Asia, and other European countries[30-32] but spanned over shorter periods of surveillance. Other identified studies either involved a mixed (adult and paediatric) population [34,35] and/or were limited to a specific aetiology (e.g. Japanese and tick-borne encephalitis).[36,37] The overall incidence rates varied between the identified studies and data from these studies are not directly applicable to the paediatric population in England. Two studies in England were identified. One was a study of hospital admissions for children with viral encephalitis only.[2] The other [3] involved a mixed population. As a result, it is not be possible to correctly estimate hospital admission rates and disease incidence for all-cause encephalitis in a solely paediatric population from both studies. Furthermore, the studies in England were conducted over a shorter period than our study, which limits their use in observing long-term admission trends in relation to the innovations in the field of encephalitis. A second search was conducted to identify studies reporting on the impact on MMR on measles or mumps encephalitis in children, using the search terms ("hospital admissions" OR "hospital admission rates" OR "admission rates" OR "hospitalisation*" OR "hospitalization*" OR "incidence" OR "incidence rates") AND ("measles encephalitis" OR "mumps encephalitis") AND ("MMR vaccin*" OR "measles vaccin*" OR "mumps vaccin*"). Two studies reporting the impact of MMR vaccination on measles encephalitis admissions in the Czech Republic, Australia and Finland were identified.[11,12,38] There were no similar studies for the paediatric population in England.

Added value of this study

Hospital admissions for encephalitis in people less than 20 years old in England are on the increase highlighting the need for close disease surveillance. Hospital admissions due to measles and mumps encephalitis have declined substantially following the introduction of the 2-dose MMR vaccination schedule. Our findings show that the age-related epidemiological profile for acute disseminated encephalomyelitis has changed and admission rates for it in the past decade have increased possibly reflecting enhanced disease identification with the use of MRI's. While admission rates for the herpesviral encephalitis have increased reflecting improved ascertainment of aetiology particularly with the use of Herpes Simplex Virus PCR, rates for encephalitis of unknown aetiology have also increased suggesting there is still room for improvement in aetiological diagnosis in children with encephalitis.

Implications of all available evidence

To the best of our knowledge, our study reports the most complete population based dataset in the UK of disease incidence for all-cause encephalitis in children in England between 1979 and 2011. It is also the first English study to demonstrate the impact of MMR vaccination on measles and mumps encephalitis admissions. Ongoing disease surveillance and identification of enhanced diagnostic techniques remain crucial.

Conflict of interests: We declare that we have no conflicts of interest

Contributors: MI conceived and designed the study. RG extracted and analysed the data. MI undertook further analyses and results were verified by AN who also provided statistical support. MI drafted the manuscript which was critically reviewed and edited by MS, MJG, RG, AN and AJP to develop the final version. MJG directed the building of the consolidated 33-year datasets and the design of trend studies using them. RG, MJG, AN and MI act as guarantors.

Data sharing statement: Summary data and analysis scripts may be available from the corresponding authors, on request.

Legend

Figure 1: Hospital admission rates for all-cause encephalitis in people aged 0-19 years

Figure 2a Hospital admission rates for measles encephalitis in people aged 0-19 years

Figure 2b: Hospital admission rates for mumps encephalitis in people aged 0-19 years

Figure 3a: Hospital admission rates for encephalitis of unknown aetiology in people aged 0-19 years in England

Figure 3b: Hospital admissions for herpes meningoencephalitis in people aged 0-19 years in England

Figure 4: Hospital admission rates for varicella and enteroviral encephalitis in people aged 0-19 years in England

Figure 5a: Hospital admissions for ADEM in people aged 0-19 years

Figure 5b: Poisson regression model for ADEM admissions in people aged 0-19 years in England

Figure 5c: Hospital admission rates for ADEM in people aged < 1 year in England

Figure 5d: Hospital admission rates for ADEM in people aged 1-9 years in England

Figure 5e: Hospital admission rates for ADEM in people aged 10-19 years in England

Table 1: International Classification of Disease (ICD) codes used to identify encephalitis admissions

Appendix

Supplementary Figure 1a: National hospital admission rates for all-cause encephalitis by age group

Supplementary Figure 1b: Poisson regression model for all-cause encephalitis admissions in people aged 0-19 years in England

Supplementary Figure 1c: Poisson regression model for all-cause encephalitis for children aged < 1 year in England

Supplementary Figure 1d: Person-based admission rates for all-cause encephalitis including and excluding short (<5days) cumulative lengths of stay

Supplementary Figure 2a: Age-specific admission rates for measles encephalitis in people aged 0-19 years in England

Supplementary Figure 2b: Age-specific admission rates for mumps encephalitis in people aged 0-19 years in England

References

1. Aygün AD, Kabakuş N, Celik I, et al. Long-term neurological outcome of acute encephalitis. *J Trop Pediatr* 2001; **47**(4): 243-7.
2. Davison KL, Crowcroft NS, Ramsay ME, Brown DW, Andrews NJ. Viral encephalitis in England, 1989-1998: what did we miss? *Emerg Infect Dis* 2003; **9**(2): 234-40.
3. Granerod J, Cousens S, Davies NW, Crowcroft NS, Thomas SL. New estimates of incidence of encephalitis in England. *Emerg Infect Dis* 2013; **19**(9).
4. Department of Health. Immunisation against infectious disease. London Stationery Office, 1996. (The "green book."), Chapter 21.
5. Jeffery KJ, Read SJ, Peto TE, Mayon-White RT, Bangham CR. Diagnosis of viral infections of the central nervous system: clinical interpretation of PCR results. *Lancet* 1997; **349**(9048): 313-7.
6. Krupp LB, Tardieu M, Amato MP, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. *Mult Scler* 2013; **19**(10): 1261-7.
7. Martin NG, Iro MA, Sadarangani M, Goldacre R, Pollard AJ, Goldacre MJ. Hospital admissions for viral meningitis in children in England over five decades: a population-based observational study. *Lancet Infect Dis* 2016.
8. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016; **15**(4): 391-404.
9. da Rocha AJ, Nunes RH, Maia AC, do Amaral LL. Recognizing Autoimmune-Mediated Encephalitis in the Differential Diagnosis of Limbic Disorders. *AJNR Am J Neuroradiol* 2015; **36**(12): 2196-205.
10. Goldacre MJ, Maisonneuve JJ. Hospital admission rates for measles and mumps in England: historical perspective. *Lancet* 2013; **382**(9889): 308-9.
11. Koskiniemi M, Vaheri A. Effect of measles, mumps, rubella vaccination on pattern of encephalitis in children. *Lancet* 1989; **1**(8628): 31-4.
12. Orlíková H, Malý M, Lexová P, et al. Protective effect of vaccination against mumps complications, Czech Republic, 2007-2012. *BMC Public Health* 2016; **16**: 293.
13. Ramsay M, Gay N, Miller E, et al. The epidemiology of measles in England and Wales: rationale for the 1994 national vaccination campaign. *Commun Dis Rep CDR Rev* 1994; **4**(12): R141-6.
14. Gay N, Miller E, Hesketh L, et al. Mumps surveillance in England and Wales supports introduction of two dose vaccination schedule. *Commun Dis Rep CDR Rev* 1997; **7**(2): R21-6.
15. Epidemiology and Prevention of Vaccine-Preventable Diseases, The Pink Book: Course Textbook - 13th Edition (2015).
16. Mumps epidemic-United Kingdom, 2004-2005. MMWR Morbidity and Mortality Wkly Rep.**February 24, 2006 / 55(07);173-175.**http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5507a1.htm.
17. Savage E, Ramsay M, White J, et al. Mumps outbreaks across England and Wales in 2004: observational study. *BMJ* 2005; **330**(7500): 1119-20.
18. NHS Imaging and Radiodiagnostic activity in England 2012/13 Release.
19. Titulaer MJ, Höftberger R, Iizuka T, et al. Overlapping demyelinating syndromes and anti–N-methyl-D-aspartate receptor encephalitis. *Ann Neurol* 2014; **75**(3): 411-28.
20. Pohl D, Alper G, Van Haren K, et al. Acute disseminated encephalomyelitis: Updates on an inflammatory CNS syndrome. *Neurology* 2016; **87**(9 Suppl 2): S38-45.
21. Raschilas F, Wolff M, Delatour F, et al. Outcome of and prognostic factors for herpes simplex encephalitis in adult patients: results of a multicenter study. *Clin Infect Dis* 2002; **35**(3): 254-60.

22. Schmidt A, Bühler R, Mühlemann K, Hess CW, Täuber MG. Long-term outcome of acute encephalitis of unknown aetiology in adults. *Clin Microbiol Infect* 2011; **17**(4): 621-6.
23. Utley TF, Ogden JA, Gibb A, McGrath N, Anderson NE. The long-term neuropsychological outcome of herpes simplex encephalitis in a series of unselected survivors. *Neuropsychiatry Neuropsychol Behav Neurol* 1997; **10**(3): 180-9.
24. Stahl JP, Mailles A. What is new about epidemiology of acute infectious encephalitis? *Curr Opin Neurol* 2014; **27**(3): 337-41.
25. Granerod J, Ambrose HE, Davies NW, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis* 2010; **10**(12): 835-44.
26. Gable MS, Sheriff H, Dalmau J, Tilley DH, Glaser CA. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. *Clin Infect Dis* 2012; **54**(7): 899-904.
27. Irani SR, Vincent A. Autoimmune encephalitis -- new awareness, challenging questions. *Discov Med* 2011; **11**(60): 449-58.
28. Thompson C, Kneen R, Riordan A, Kelly D, Pollard AJ. Encephalitis in children. *Arch Dis Child* 2012; **97**(2): 150-61.
29. Kneen R, Michael BD, Menson E, et al. Management of suspected viral encephalitis in children - Association of British Neurologists and British Paediatric Allergy, Immunology and Infection Group national guidelines. *J Infect* 2012; **64**(5): 449-77.
30. Britton PN, Khoury L, Booy R, Wood N, Jones CA. Encephalitis in Australian children: contemporary trends in hospitalisation. *Arch Dis Child* 2016; **101**(1): 51-6.
31. Koskiniemi M, Korppi M, Mustonen K, et al. Epidemiology of encephalitis in children. A prospective multicentre study. *Eur J Pediatr* 1997; **156**(7): 541-5.
32. Ishikawa T, Asano Y, Morishima T, et al. Epidemiology of acute childhood encephalitis. Aichi Prefecture, Japan, 1984-90. *Brain Dev* 1993; **15**(3): 192-7.
33. Burns EM, Rigby E, Mamidanna R, et al. Systematic review of discharge coding accuracy. *J Public Health (Oxf)* 2012; **34**(1): 138-48.
34. George BP, Schneider EB, Venkatesan A. Encephalitis hospitalization rates and inpatient mortality in the United States, 2000-2010. *PLoS One* 2014; **9**(9): e104169.
35. Khetsuriani N, Holman RC, Anderson LJ. Burden of encephalitis-associated hospitalizations in the United States, 1988-1997. *Clin Infect Dis* 2002; **35**(2): 175-82.
36. Pazdiora P, Štruncová V, Švecová M. Tick-borne encephalitis in children and adolescents in the Czech Republic between 1960 and 2007. *World J Pediatr* 2012; **8**(4): 363-6.
37. Hsu LC, Chen YJ, Hsu FK, et al. The incidence of Japanese encephalitis in Taiwan--a population-based study. *PLoS Negl Trop Dis* 2014; **8**(7): e3030.
38. Tobin S, Kelly H. Measles encephalitis in Victoria, 1962-96: down but not out. *Aust N Z J Public Health* 1999; **23**(4): 443.